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Prevalence of human papillomavirus genotypes in HIV-1-infected women in Seattle, USA and Nairobi, Kenya: results from the Women's HIV Interdisciplinary Network (WHIN)

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Summary

Background—HIV-infected women have a high prevalence of human papillomavirus (HPV) infection and are more likely to be infected with HPV genotypes that are considered high-risk and have the potential for progressing to cervical cancer. The currently available HPV vaccines protect against specific HPV genotypes that may not be the most important causes of dysplasia and potentially of cervical cancer in HIV-1-infected women. African women have been underrepresented in the studies of global prevalence of HPV genotypes.

Methods—We compared the HPV genotype distribution in HIV-1-infected women from Seattle, Washington, USA and Nairobi, Kenya. The reverse line blot assay and DNA sequencing on cervicovaginal lavage (CVL) specimens were carried out.

Results—The most commonly detected HPV types among the women from Seattle were HPV 56, 66, MM8, and 81; in contrast HPV 53, 33, and 58 were the most common HPV genotypes detected

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Ethical approval: The protocol was approved by the research subjects review boards (RSRB) of the University of Rochester in Rochester, NY, USA, the University of Washington in Seattle, WA, USA, and the Kenya Medical Research Institute in Nairobi, Kenya. Written informed consent was obtained from all patients who participated in this study.

Conflict of interest: We have no conflict of interest for this work.

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in the CVL specimens from the women in the Nairobi cohort. The HPV types associated with low-grade squamous intraepithelial lesions (LSIL) were HPV 53 and HPV 56. HPV types 58, 52, and 16 were associated with high-grade squamous intraepithelial lesions (HSIL).

Conclusions—A better understanding of HPV genotype distribution in the most affected regions of the world is essential to planning effective vaccine strategies if we are unable to demonstrate cross-protection between HPV genotypes included in the present vaccines and those prevalent in the different populations.

Keywords

HPV genotypes; HIV-infected women; Cervical dysplasia

Introduction

With the recent introduction of two human papillomavirus (HPV) vaccines, the acquisition of knowledge regarding the distribution of HPV genotypes among geographic and biological subgroups has become increasingly important. While the efficacy of both the bivalent (Cervarix; GlaxoSmithKline) and quadrivalent (Gardasil; Merck and Co., Inc.) vaccines has been well documented,[1–5] the effectiveness of these vaccines in curbing the incidence of cervical cancer will be dependent, in large part, upon the prevalence of oncogenic vaccine genotypes (HPV 16 and 18) in a given population.

Global prevalence studies suggest that the two oncogenic HPV genotypes included in the available vaccines, HPV 16 and 18 (the quadrivalent vaccine also protects against HPV 6 and 11, which cause genital warts but are low risk with regards to cervical cancer), account for approximately 70% of cervical cancer worldwide.[6–8] Extrapolating from this data, it is easy to conclude that the widespread use of the highly efficacious current vaccines has the potential to decrease the incidence of cervical cancer by a similar percentage. Unfortunately, as data describing the distribution of HPV genotypes among subgroups of women from different geographic regions and with different co-morbidities, such as HIV-1 infection, accumulates, the relative prevalence of oncogenic vaccine genotypes compared with non-vaccine oncogenic genotypes among these groups is seen to lessen and the potential impact of the current vaccines to diminish correspondingly.

We compared the HPV genotype distribution between HIV-1-infected women from Seattle, Washington, USA and Nairobi, Kenya in order to assess the prevalence of HPV genotypes in two geographically distinct populations when superimposed upon the impact of HIV-1 co-infection.

Materials and methods

Study subjects

HIV-1-infected women were recruited from the Northwest Family Center, Madison Clinic and from the University of Washington Adult AIDS Clinical Trials Units (ACTU), which are located at Harborview Medical Center in downtown Seattle and together provide medical care for about 225 women annually. Nairobi women were enrolled from the Center for Respiratory Disease Research at the Kenya Medical Research Institute in Nairobi, Kenya, where 250 HIV-1-infected women are followed. Pre-menopausal women between the ages of 13 and 50 years with a documented HIV-1 infection who were able to provide informed consent and did not have a history of hysterectomy or high-grade squamous intraepithelial lesions (HSIL) on cervical cytology were invited to participate. A total of 38 women from the Seattle site and 50 women from Nairobi agreed to participate in the study. Women from Nairobi were required

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to have a CD4+ cell count of ≥350 cells/mm^3, but there were no restrictions on CD4+ cell count for women in the Seattle cohort.

After completing informed consent procedures, study subjects underwent a standardized history and physical examination. A questionnaire, administered to all study subjects, included questions regarding lifetime number of sexual partners, condom use, and oral contraceptive use.

Collection of specimens

Subjects collected a urine sample for amplification testing for chlamydia and gonorrhea detection. Specimens of cervical cells were obtained using the Cervex-Brush (Rovers Medical Devices) and spatula for the exocervix. Cervicovaginal lavage (CVL) was performed using 10 ml of phosphate-buffered saline (PBS) placed in a syringe attached to a plastic pipette. The cervix was bathed three times and liquid was collected from the posterior fornix using the same syringe. CVL specimens were frozen in aliquots at −70°C, shipped in dry ice, and stored at −70°C until HPV DNA testing was performed.

Blood was collected for CD4+ cell counts, and was processed at each site. For HIV RNA determinations, blood was collected into vacutainer ethylenediaminetetraacetic acid (EDTA) tubes and separated within 6 h of collection. Plasma samples from study participants at the Nairobi site were frozen at −80°C and shipped on dry ice to the University of Washington in Seattle for processing.

Specimen processing

Urine was tested, at each site, by similar amplification methods for gonorrhea and chlamydia.

Lymphocyte markers (CD4+ counts) were determined by standard flow cytometric methods at either the Kenya Medical Research Institute in Nairobi or the University of Washington in Seattle.

For both cohorts, plasma was processed at the University of Washington in Seattle and HIV RNA measured using a real-time reverse transcriptase PCR (real-time RT-PCR) with a detection limit of 30–1 000 000 copies/ml (bioMérieux, Inc., Durham, NC, USA).

For cervical cytology, slides were read by local staff pathologists at the respective sites and results were reported according to the 2001 Bethesda System for cervical cytology reporting. Pap smears were considered abnormal if they contained atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL).

Testing of CVL samples for HPV genotypes

Total DNA was extracted from each lavage specimen using a commercial kit (Epicentre Technologies, Madison, WI, USA).

PCR amplification was performed by adding purified specimen total DNA to previously prepared buffer containing Amplitaq Gold (Applied Biosystems, Foster City, CA, USA), MY09/MY11 primers, and human β-globin primers.[9] PCR reaction products were analyzed by agarose gel electrophoresis, and amplified products were detected by staining with ethidium bromide. Specimens were scored positive if they contained amplification products of expected sizes for both MY09/11 and β-globin amplicons. Samples meeting these criteria were then subjected to genotype analysis.

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The reverse line blot assay was performed using a modification of previously described methods.[9,10] Each amplified biotinylated product was hybridized to a set of 27 immobilized oligonucleotide probes, each corresponding to an individual HPV genotype. Specimens positive for HPV DNA by PCR but negative by reverse line blot were sequenced.

Statistical analyses

Differences between cities in baseline demographic variables were assessed using a *t*-test, a Wilcoxon rank sum test, or Fisher's exact test, as appropriate to the data. To discern the relationship between HPV genotypes, geographical location, and cervical cytology, proportions of patients with abnormal Pap smears with their 95% confidence intervals (95% CI), employing the asymptotic standard error, are reported. These proportions were assessed for first visit data for those patients with CD4+ counts >350 cells/mm^3. In an attempt to summarize the associations, exploratory logistic regressions evaluated the regression of the cervical cytology variable dichotomized to represent any type of abnormal Pap smear vs. results that were within normal limits on categorized HPV type, trichotomized as no HPV type, only low-risk HPV type, or high-risk HPV type. Cervical cytology was also regressed on number of HPV types, which were categorized as none, single HPV type, or more than one HPV type. The association of cervical cytology and cohort was also evaluated.

Results

Study population

Among the 38 women enrolled in Seattle, 20 (53%) were African American, 12 (32%) were Caucasian, two (5%) Asian or Pacific Islander, two (5%) Hispanic, one (3%) Native American, and one of unspecified race/ethnicity (3%). The mean age at enrollment for this group was 38.3 ± 6.6 years, the median CD4+ cell count was 346 cells/mm^3, and the median HIV RNA was 1036 copies/ml of plasma. The 50 women enrolled in Nairobi had a mean age at enrollment of 32.7 ± 5.0 years, had a median CD4+ cell count of 538 cells/mm^3, and a median HIV RNA of 13 942 copies/ml. Among women in the Nairobi cohort, 24 (48%) identified themselves as belonging to the Kikuyu ethnic group, eight (16%) to the Luo, six (12%) to the Luhya, and three (6%) to the Kamba; nine (18%) were listed as 'unknown ethnic group' or 'other'. All of the women in the Nairobi cohort reported acquiring HIV exclusively via heterosexual sex, in contrast to the Seattle group in which 25 (66%) women reported heterosexual contact as their HIV risk factor, nine women (24%) reported injection drug use as their risk factor, two women (5%) reported receipt of blood products as their only HIV risk factor, and two women (5%) reported no HIV risk factor. The use of oral contraceptives at any given time was reported by 29 women (76%) in the Seattle group and 30 women (60%) in the Nairobi group. Only two women (5%) in the Seattle group and two (4%) in the Nairobi group reported taking oral contraceptives at the time of study. The median number of lifetime sexual partners was 11 (5–20) for the Seattle group and 3 (2–5) for the Nairobi group. All women in the Nairobi group were untreated, while 20 women (53%) in the Seattle group were receiving antiretroviral therapy. The number of sexual partners ($p = 0.04$), CD4+ cell count ($p = 0.008$), and antiretroviral treatment ($p < 0.0001$) were significantly different between the groups at baseline (Table 1).

HPV genotypes

Eighty-four CVL samples collected from 35 of the 38 women enrolled in Seattle and 49 of the 50 women enrolled in Nairobi were tested for HPV genotypes. Of the 35 specimens available from the Seattle cohort, 20 were β-globin-positive and nine were HPV DNA-positive. Of the 49 samples available from women in the Nairobi cohort 37 were β-globin-positive and 11 were HPV DNA-positive.

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Nine out of 35 (26%) CVL samples from women in the Seattle cohort were positive for HPV DNA; a single HPV genotype was detected in 3/9 (33%) positive CVL samples, dual HPV genotypes were detected in 2/9 (22%) samples, and one sample had three HPV genotypes detected. Three out nine (33%) samples had non-typeable HPV DNA by reverse line blot and were sequenced and reported as having a single HPV type each. Eleven out of 49 CVL samples (22%) were positive for HPV DNA among women from the Nairobi cohort; a single HPV genotype was identified in 9/11 (82%), dual HPV genotypes detected in one sample, and one had triple HPV genotypes detected (Table 2).

The most common HPV genotypes detected in the specimens from the Seattle cohort were HPV 56, 66, MM8, and 81, which were detected in two samples each, followed by HPV 6, MM7, 33, 70, and 16 in one sample each. The most common HPV genotypes detected in the CVL specimens from the Nairobi cohort were HPV 53, which was detected in 3/11 (27%) samples containing HPV DNA, followed by HPV 33 in two samples (18%) and HPV 58 in two samples (18%). HPV 16, 18, 62, and MM8 were found in one sample each (9%) (Table 2).

Pap smear results and HPV genotypes

Thirty-seven Pap smears were available from the 38 women enrolled in Seattle and 46 Pap smears were available from the 50 women enrolled in Nairobi. Three Pap smears were deemed inadequate for interpretation in the Nairobi group and one specimen was missing in each cohort. We found a similar proportion of subjects with cervical smear abnormalities across sites, with 12% of the women in the Seattle group and 11% of the women in the Nairobi group.

HPV types associated with LSIL were HPV 53 and HPV 56, while HPV 58, 52, and 16 were associated with HSIL. The summary results for HPV types are reported in Table 3. An increase in the proportion of abnormal cervical smears is seen as the number of HPVs increases, from no HPV types to one HPV type to more than one HPV type. Similarly there is an increase in the proportion of patients with abnormal Pap smear results that follows the progression from no HPV infection to infection with low-risk HPV to infection with high-risk HPV.

Women with more than one HPV type detected in CVL were 22.5 times more likely to have an abnormal Pap smear than those with no HPV detected. Results of the univariate logistic regression are reported in Table 4 and point to the increased odds for an abnormal Pap smear given more than one HPV type, as well as in the presence of high-risk HPV. Looking at the association of any risk (that is, low- or high-risk HPV) vs. no risk, reveals an odds ratio (OR) of 7.03 (95% CI 1.55–32.00, $p = 0.01$). No association between Pap smear results and cohort (Seattle vs. Nairobi) was found (OR 0.74, 95% CI 0.14–4.00, $p = 0.73$).

Discussion

In this study of two geographically distinct cohorts of HIV-1-infected women, we detected multiple HPV genotypes in three out of nine (33%) CVL specimens positive for HPV DNA collected from women enrolled in Seattle, while only two out 11 (18%) CVL specimens positive for HPV DNA from women from Nairobi had multiple HPV detected. The most common HPV genotypes detected among the Seattle cohort were 56 (22%), 66 (22%), MM8 (22%), and 81 (22%); HPV 70, 6, 16, 33, and MM7 were found in 11%. The most common HPV types detected in CVL specimens from the Nairobi cohort were HPV 53 (27%), followed by HPV 33 (18%) and HPV 58 (18%), with HPV 16, 18, 62 and MM8 detected in only 9%. Patients from both cohorts of this study had prevalence of high-risk HPV types other than 16 and 18.

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Abnormalities were noted in 8/37 Pap smears (22%) obtained from the Seattle cohort and in 12/46 Pap smears (26%) from the Nairobi cohort. There were differences in the abnormalities on cervical cytology between cohorts. For the Seattle group, ASCUS was reported in 50% of the abnormal Pap smears at initial visit, LSIL in 37.5%, and HSIL in 12.5%, while in the Nairobi cohort 17% of the abnormal Pap smears were reported as ASCUS, 25% as HSIL, and 17% as LSIL. Of the abnormal Pap smears, 42% were classified as 'other' (either reactive or regenerative changes). HPV types associated with LSIL were HPV 53 and 56; HPV types 58, 52, and 16 were associated with HSIL. When comparing abnormalities in Pap smears using the data from only those women in the Seattle cohort whose CD4+ cell count was over 350 cells/mm^3 and thus similar to the women from Nairobi for whom a CD4+ cell count over 350 cells/mm^3 was part of the entry criteria, we found a similar proportion of subjects with cervical smear abnormalities across sites, with 12% of the women in the Seattle group and 11% of the women in the Nairobi group.

Inspection of the proportions in Table 3 and the odds ratios in Table 4 demonstrates that women with more than one HPV type detected in CVL were 22.5 times more likely to have an abnormal Pap smear than those with no HPV detected. Women were 7.50 times more likely to have an abnormal Pap smear when they had high-risk HPV present vs. none. These results should be interpreted with caution, given the very large 95% CI, which reflect a small sample size. This qualification holds true for the reported proportions as well, where the 95% CI are also broad.

In light of the aforementioned caveat, we note that the results of this current study are in concordance to our previous study of HPV genotype distribution among HIV-infected women from Rochester, NY, in which HPV 16 and HPV 18 were found to be only the 3rd and 9th most prevalent high-risk HPV genotypes, respectively.[11] Our results are also in agreement with a meta-analysis that included data from over 5500 HIV-infected women, in which several non-vaccine oncogenic HPV genotypes were found to be more prevalent than HPV 16 among HIV-infected women with HSIL, including genotypes 51, 52, and 58.[12] Moreover, a distribution of high-risk HPV that demonstrates a decreased relative prevalence of vaccine types has been confirmed in other African studies.[13–20]

The cause for the predominance of multiple HPV infections in the Seattle cohort is not completely clear but may be due in part to the number of lifetime sexual partners, as participants from Nairobi had significantly fewer sexual partners (median lifetime sexual partners 3, interquartile range (IQR) 2–5) than the participants from Seattle (median life time sexual partners 11, IQR 5–20). The difference in median CD4+ cell count was also significantly different. Preserved cellular immunity as measured by CD4+ cell count may also have influenced the prevalence of multiple HPV infection, with women from Nairobi having higher CD4+ cell counts and lower prevalence of HPV infections with multiple HPV types. The most common HPV genotypes detected were also different in the two groups of women. Nevertheless, both cohorts in this study had a higher prevalence of high-risk HPV types other than HPV 16 and 18. Interestingly, the relationship between immunosuppression (low vs. high CD4+ cell counts) and HPV 16 has been reported as less pronounced than for other HPV types.[21] This was not evident in our study; however our numbers are small and do not allow firm conclusions in this regard.

The vast majority of global prevalence data for HPV genotypes are based on studies of women from Europe and North America. It is in the developing world, however, where most deaths from cervical cancer occur.[22,23] Africa in particular has been underrepresented in available data. Still, although African women only accounted for 6% of cases in a meta-analysis of worldwide distribution of HPV genotypes among women with cervical cancer, these women were still found to have the lowest proportion of cervical cancer cases attributable to HPV 16/18.[7]

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A more detailed understanding of HPV genotype distribution in resource-poor regions of the globe is essential to planning effective vaccine strategies, in particular if we are unable to demonstrate cross-protection between HPV genotypes included in the present vaccines and those prevalent in the different populations.

Studying HPV in African women provides an opportunity to assess the additive impact of HIV and regional differences in HPV genotype distributions, and will assist with the development of vaccine strategies that are appropriate for this population.

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Table 1

Baseline characteristics of the study population, stratified by site

	Seattle (*n* = 38)	**Nairobi (*n* = 50)**
Age (years) mean ± SD	38.3 ± 6.6	32.7 ± 5.0
Parity	2.5 ± 2.1	2.6 ± 2.3
Race/ethnicity, *n* (%)		
Caucasian	12 (32)	-
African American	20 (53)	-
Asian/Pacific Islander	2 (5)	-
Hispanic	2 (5)	-
Native American	1 (3)	-
Other	1 (3)	-
Kikuyu		24 (48)
Luo		8 (16)
Luhya		6 (12)
Kamba		3 (6)
Other/unknown		9 (18)
HIV risk factor, *n* (%)[a]		
IVDU	9 (24)	
Heterosexual	25 (66)	
Blood transfusion	2 (5)	
Other/unknown	2 (5)	
Lifetime sexual partners		
Median (IQR)	11 (5–20)	3 (2–5)[b]
Oral contraceptive use, *n* (%)		
Ever	29 (76)	30 (60)
Current	2 (5)	2 (4)
On ARVT, *n* (%)	20 (53)	0 (0)[c]
CD4+ cell count (cells/mm^3), median (range)	346 (30–1168)	538[d] (353–1316)
HIV RNA (copies/ml), median (range)	1036 (<30–277 000)	13 942 (<30–588 000)

SD, standard deviation; IVDU, intravenous drug use; IQR, interquartile range; ARVT, antiretroviral therapy.

[a]Nairobi women had acquired HIV exclusively by heterosexual transmission.

[b]$p = 0.04$, Wilcoxon rank-sum test.

[c]$p < 0.0001$, Fisher's exact test.

[d]$p = 0.008$, Wilcoxon rank-sum test.

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Table 2

Results of HPV genotypes at initial visit, by site

Cohort	Number of CVL samples	HPV infections	HPV types at initial visit (number of occurrences)
Seattle (*n* = 37)	35	Triple: 1 Dual: 2 Single: 6	**56** (2), **66** (2), MM8 (2), 81 (2), 70 (1), 6 (1), **16** (1), **33** (1), MM7 (1)
Nairobi (*n* = 50)	49	Triple: 1 Dual: 1 Single: 9	**53** (3), **33** (2), **58** (2), **16** (1), **18** (1), 62 (1), MM8 (1)

HPV, human papillomavirus; CVL, cervicovaginal lavage.

Numbers in bold type denote high-risk HPV types.

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Table 3

Proportion of women with abnormal cytology at initial visit by HPV number and type and by city (subjects with CD4+ cell counts ≥350 cells/mm^3 only)

	Proportion of abnormal Pap smears	95% confidence interval
Number of HPVs		
No HPV type	0.08	0.01–0.16
Single HPV type	0.27	0.01–0.54
>Single HPV type	0.67	0.13–1.00
HPV type		
No HPV type	0.08	0.01–0.16
Only low-risk HPV	0.33	0.00–0.87
High-risk HPV	0.40	0.10–0.70
Cohort		
Seattle	0.11	0.00–0.27
Nairobi	0.15	0.05–0.26

HPV, human papillomavirus.

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Table 4

Association of Pap smear results and HPV genotypes at initial visit for subjects with CD4+ cell counts ≥350/mm^3

	OR[a]	95% CI	*p*-Value
Number of HPVs			
Single HPV type vs. no HPV type	4.22	0.79–22.53	0.09
>Single HPV type vs. no HPV type	22.50	1.66–305.73	0.02
HPV type			
Only low-risk HPV vs. no HPV	5.63	0.42–76.43	0.19
High-risk HPV vs. no HPV	7.50	1.47–38.15	0.02

OR, odds ratio; CI, confidence interval.

[a]OR reflects the odds of an abnormal Pap smear.